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Towards quantitative uncertainty assessment for cancer risks: Central estimates and probability distributions of risk in dose–response modeling ☆

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Abstract

Regulatory agencies and the scientific community have been engaged in a long-term effort to strengthen health risk assessment procedures. Recently the momentum of this effort has accelerated to increasing biological information for a variety of toxic compounds and emphasis on the policy goal of broader characterization of scientific uncertainty (in contrast to providing only a single risk estimate). For example, the OMB Regulatory Analysis Guidelines [OMB, 2003. Office of Management and Budget. Circular A-4. Available from: <http://www.whitehouse.gov/omb/circulars/a004/a-4.html/>] suggest that a formal quantitative uncertainty analysis be performed for economic assessments in support of major regulatory analyses, a process that can utilize both expected values and probability distributions for risk estimates. Some efforts have been made in the past to provide probability distributions of risk estimates. In this article, we examine a procedure for constructing probability distributions and expected values of risk estimates using a Bayesian framework. This approach has the advantage of mathematical soundness and computational feasibility, given the Markov chain Monte Carlo software tools that are available today. Importantly, the Bayesian framework can serve as a unifying platform for uncertainty analysis in cancer risk assessment. This paper provides some initial applications of Bayesian methods in quantitative analysis of uncertainty in cancer risk assessment, including implementation with cancer dose–response data sets for two chemicals. The Bayesian expected risk calculations provide an approach to generating a central estimate of risk that does not have the instability problems that have often limited utility of MLE risk estimates.
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1. Introduction

Using cancer risk assessment to estimate risks from environmental pollutants is controversial, in part, because of uncertainty about shape of the dose–response relationship between the control group and the lowest tested concentration. However, environmental decision-making regarding chemical exposures frequently depends on these estimates of risks at exposures far below the range of the exposure in the experiment. Since publication of the important National Research Council Risk Assessment document (NRC, 1983), risk assessment has evolved to emphasize incorporation of more scientific information in dose–response modeling. However, biologically based modeling is often limited by the lack of crucial information about mechanism of carcinogenic action at low doses to which humans are exposed. For this reason, empirical statistical modeling of observed dose–response relationships continues to be a necessary approach for most cancer risk assessments. We anticipate that for the foreseeable future,

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applied dose–response assessments will utilize both descriptive statistical and more biologically based methodologies. In both cases significant uncertainties may exist.

Currently the risk assessment community is striving to characterize uncertainty more explicitly and quantitatively in important assessments. The OMB Regulatory Analysis Guidelines (OMB, 2003) suggest that a formal quantitative uncertainty analysis be performed for economic assessment in support of major regulatory analyses, a process that can utilize a probability distribution of the cancer risk estimate and the expected value of risk. The current EPA cancer guidelines (USEPA, 2005) also recommend that all risk assessments identify and characterize uncertainties in risk estimates wherever possible. To go beyond traditional approaches of uncertainty analysis, such as analysis of sensitivity, a more conceptually consistent and coherent system must be developed. The importance of developing such a system is underscored by the fact that "uncertainty" involves multi-layers of factors even though the ultimate focus is always about the risk estimate due to exposures to a suspected carcinogenic agent. For instance, uncertainty of risk estimates could arise from the choice of dose–response models, assumptions about mode of action, database, age, gender, etc. The Bayesian framework provides a natural platform for integrating different factors in risk assessment. As an initial step towards a broader uncertainty analysis in the future, in this paper, we focus on the dose–response modeling aspect, and provide some insights into the potential of further work.

Currently, the most frequently used EPA approach to estimate cancer risk at low doses (USEPA, 2005) is based on a linear extrapolation from a "point of departure" (POD). For animal studies, POD is typically a lower bound ($BMDL_{10}$) on the benchmark dose (BMD_{10}) associated with a 10% extra risk of tumors. Typically, dose–response in the range of the experimental data is modeled using the multistage model, $P(d) = 1 - \exp(-(q_0 + q_1 d + \cdots + q_k d^k))$, where d is dose, and q_i's are non-negative parameters to be estimated. Then, a straight line slope from the ($BMDL_{10}$, BMR) to the origin $(0,0)$ produces a "model-free" estimate of extra risk. This result is interpreted as a reasonable upper bound estimate of risk. The previous EPA approach extrapolated the multistage model estimate to low doses, but utilized only the upper confidence limit (rather than the MLE), since MLE estimates of q_i's, in particular q_1, can be very unstable at the boundary of the parameter space and lead to unstable model-based estimates of low-dose risk based on the MLE. The ML routine is essentially choosing the best model, by zeroing out parameters if they go outside their bound; because of this choice uncertainty results.

As risk assessment has evolved over time, it has been recognized that there is value in providing, when feasible, more detailed information to characterize cancer risks, including distribution of the risk and central estimate of risk (e.g. expected value, median, mode). An expected value estimate of risk is often desired for use in cost-benefit analysis, such as to compare the expected number of cancers in an exposed population to the expected economic costs of reducing such risk. All of these efforts require more than a single number approach to risk assessment.

There have been scattered activities on deriving distributions of risk estimates from dose–response modeling in the last two decades. For instance, bootstrap, Monte-Carlo methods, and asymptotic distribution of log-likelihood have been used to generate probability distributions of risk estimate (e.g. Smith and Sielken, 1988; Thompson et al., 1992; Finkel, 1995; Cox, 1996; California EPA, 2005).

The objective of this paper is to discuss a Bayesian approach to generating a probability distribution of risk estimates and deriving central estimates within a chosen model. To give proper credit, we want to point out that the posterior mean under the Bayesian framework proposed in this article coincides with an unpublished work by Dr. Todd Thorslund done in the 1980s. In this work, an averaged likelihood method was used to generate risk estimates in simple modeling situations. However, at that time, the computation was found to be difficult, if not impossible, when there were multiple parameters in the model.

The current paper applies formal Bayesian methods to evaluate the uncertainty in dose–response models. Although conceptually simple, this approach relies on the recent advances in computation using MCMC methods. This analysis takes advantage of the computational power of WinBugs 1.4.1, free software (Spiegelhalter et al., 2003) for the Bayesian analysis of statistical models using Markov chain Monte Carlo (MCMC) methods (e.g. Smith and Gelfand, 1992; Casella and George, 1992; Chib and Greenberg, 1995; Brooks, 1998; Gilks et al., 1998).

2. A Bayesian method

Consider a family of probability density or probability mass functions $f(\text{data}|q_0, q_1, \ldots, q_k)$, where $q_0, q_1, \ldots, q_k$ are parameters. With data fixed, as a function of parameters, $f(q_0, q_1, \ldots, q_k|\text{data})$ is called a likelihood function, $L(q_0, q_1, \ldots, q_k)$. The data can be in the form of tumor incidence or time-to-tumor data and the likelihood is binomial

$$L(q_0, \ldots, q_k) = \prod_{d[\text{i}]:\,\text{doses}} B(\text{Ni}, \text{Xi}) * \text{Prob}(d[\text{i}], q_0, \ldots, q_k)^{\text{Xi}} \times (1 - \text{Prob}(d[\text{i}], q_0, \ldots, q_k))^{\text{Ni}-\text{Xi}},$$

where B(Ni,Xi) is the binomial coefficient, Ni is the number of animals in dose group i and Xi is the number of responses in dose group i.

Let $P(q_0, q_1, \ldots, q_k)$ be the prior distribution of $(q_0, q_1, \ldots, q_k)$.

Since we do not have prior knowledge about $(q_0, q_1, \ldots, q_k)$ we assume a flat prior,

$$P(q_0, q_1, \ldots, q_k) \propto c, \quad \text{a constant},$$

but other diffuse priors could also be used (see Section 3). Thus, posterior distribution of $q_0, q_1, \ldots, q_k$ is $P(q_0, q_1, \ldots, q_k|\text{data}) \propto L(q_0, q_1, \ldots, q_k)$ from which the expected value of a function of parameters $q_0, q_1, \ldots, q_k$ can be calculated.

Of particular interest to us is extra risk for fixed dose d: $R(d) = (\text{Prob}(d) - \text{Prob}(0))/(1 - \text{Prob}(0))$, that is a function of parameters $q_1, q_2, \ldots, q_k$. In case of multistage model, for fixed dose d, when starting with the flat prior, the posterior is proper and the posterior mean of extra risk $E(R(q_1, \ldots, q_k, d)|\text{data})$ equals

$$E[R(d)|\text{data}] = \frac{\int \ldots \int R(q_1, \ldots, q_k, d) * P(q_0, q_1, \ldots, q_k|\text{data}) dq_0 dq_1 \ldots dq_k}{\int \ldots \int P(q_0, q_1, \ldots, q_k|data) dq_0 dq_1 \ldots dq_k} \quad (1)$$

This is true not only for the multistage model, but also for other type of models.

As noted above, mean or "expected value" risk estimates are often sought for purposes of analyses to support decision making (e.g. cost-benefit analyses). In addition to mean estimates, median estimates can also be developed using the Bayesian methodology. The calculation of estimate [1] can be easily implemented using WinBugs, as demonstrated in the examples.

3. Examples

Two examples with different dose–response characteristic are used to demonstrate risk estimation for a chosen model. The results for both examples are obtained based on convergence of three chains with different initial values, and 10,000 burn-in (i.e. the first 10,000 samples discarded) from 100,000 simulations each, using WinBugs 1.4.1, on a desktop PC, taking less than 65 s for each of the examples. The resultant posterior distribution is obtained from the combined (270,000) samples retained from the three chains. In these examples, the absolute value of WinBugs density dflat()—a uniform prior over the whole real line—was used as a prior for the coefficients in the multistage model. A diffuse normal prior constrained to be non-negative produced essentially the same results. These continuous priors do not put point mass at 0, and if point mass at 0 is appropriate (e.g. for background rate parameter) a reversible jump algorithm (e.g. Green, 1995; Brooks et al., 2003) can be used. The doses at which distribution of extra risk is calculated were chosen so that mean extra risk would be on the order of 1E−6. The MLE of extra risk under multistage model at a given dose and BMD-based (straight line) estimates of extra risk are obtained by using BMDS software (EPA, http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20167).

Confidence intervals for MLE were derived using parametric bootstrap with 10,000 simulations.

3.1. Example 1

Naphthalene: respiratory epithelial adenomas in male rats (Abdo et al., 2001). The dose–response in this example is gradual (Table 1). In situations like this, the MLE is usually stable for small changes in incidence outcomes, as is illustrated in Table 1 by changing the results of two doses

Table 1
Comparison of extra risk estimates by different methods using original naphthalene dose–response data and altered data with one tumor moved

Dose	Original data	One tumor moved
0	0/49	0/49
10	6/49	7/49
30	8/48	8/48
60	15/48	14/48
Extra risk at 5.0 E−4 ppm		
MLE-based risk 90% CI	3.5 E−6 (9.5 E−7; 4.5 E−6)	3.5 E−6 (1.1 E−6; 4.4 E−6)
BMD_{10}-based risk 90% CI	3.3 E−6 (2.2 E−6; 4.4 E−6)	3.3 E−6 (1.9 E−6; 4.4 E−6)
Posterior mean	1.9 E−6	2.0 E−6
Posterior median 90% CI	1.9 E−6 (3.3 E−7; 3.5 E−6)	2.0 E−6 (3.7 E−7; 3.7 E−6)

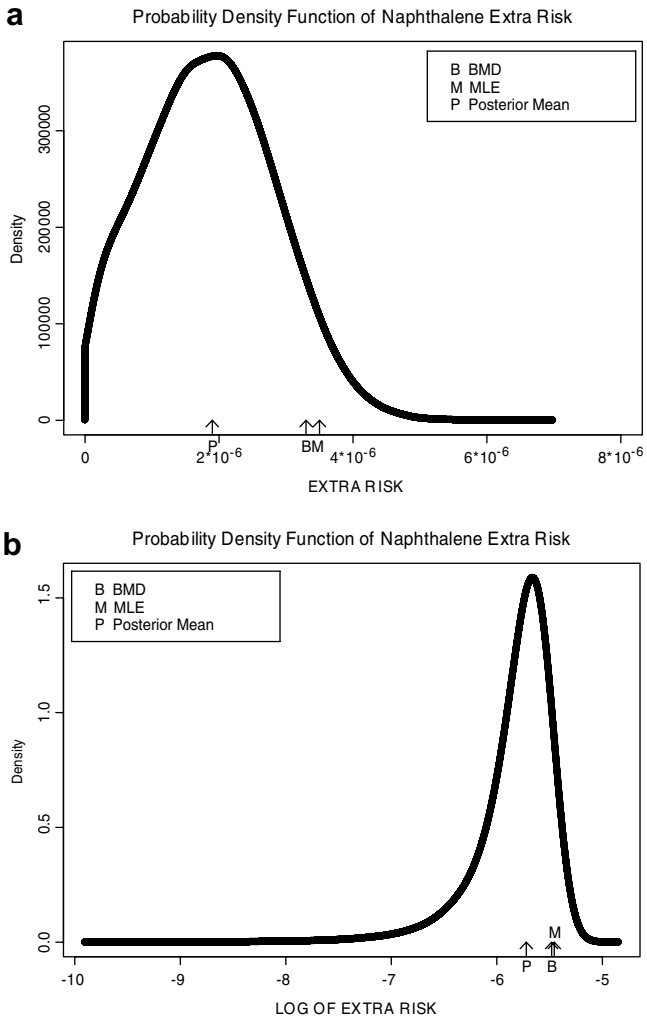

Fig. 1. Probability density function (pdf) of extra risk for naphthalene example (original data). Panel a in ordinary scale, panel b in logarithmic scale.

Table 2
Comparison of extra risk estimates by different methods using original formaldehyde dose–response data and altered data with one tumor moved

Dose	Original data	One tumor moved
0	0/341	0/341
0.07	0/107	0/107
2	0/353	1/353
6.01	3/343	3/343
9.93	22/103	22/103
15	162/386	161/386
Extra risk at 1.0 E−3 ppm		
MLE-based risk	4.5E−14	4.5E−7
90% CI	(0; 6.0E−7)	(0; 1.7E−6)
BMD_{01}-based risk	2.1E−6	2.2E−6
90% CI	(1.8E−6; 2.5E−6)	(1.8E−6; 3.0E−6)
Posterior mean	6.0E−7	8.0E−7
Posterior median	4.3E−7	6.0E−7
90% CI	(3.3E−8; 1.8E−6)	(4.9E−8; 2.2E−6)

by one tumor. Estimates obtained by the three approaches (MLE-based, BMD-based straight line approach and Bayesian analysis) exhibit little to no difference. The probability density of risk for the original data is shown in Fig. 1 (panel a) and is between approximately E−7 and E−5 (panel b).

3.2. Example 2

Formaldehyde: squamous cell carcinomas in rats (combined data from Kerns et al., 1983; Monticello et al., 1996). The dose–response is very steep above 6 ppm (Table 2). As this would suggest, estimates of some of the parameters of multistage model are on the boundary and the MLE of extra risk at 1E−3 ppm is unstable. It changes seven orders of magnitude with small changes in the incidence data. The Bayesian estimates of extra risk at 1E−3 ppm as well as straight line, BMD_{01}-based estimates are stable. The probability density of extra risk for the original data is shown in Fig. 2 (panel a) and is spread more widely than the first example (panel b).

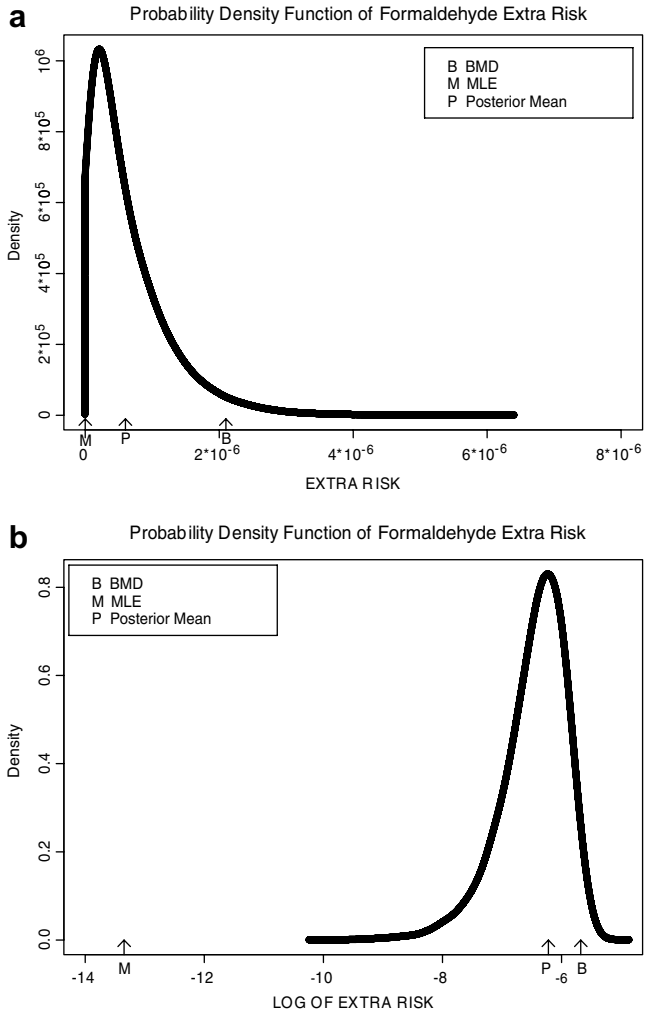

Fig. 2. Probability density function (pdf) of extra risk for formaldehyde example (original data). Panel a in ordinary scale, panel b in logarithmic scale.

4. Discussion

In this article, an application of Bayesian methods to calculate expected values and probability distributions for cancer risk estimates is proposed. Two examples given in this article suggest that the method is insensitive to the choice of diffuse priors and robust against small changes in the data. In particular, the Bayesian expected risk calculations provide an approach to generating a central estimate of risk that does not have the instability problems that have often limited utility of MLE risk estimates. Advantages of the proposed model are that the concept can be easily extended to a more general case, such as Bayesian hierarchical model with covariates (multi-layer of factors), and computation is easy to implement. When several data sets are available for the same chemical, the posterior from the first data set obtained using flat prior could be updated using newer data sets.

In addition to using bootstrap methods to generate probability distributions of risk estimates, a decision-tree approach has also been proposed by some authors (e.g. Evans et al., 1994) to provide a set of risk estimates that can address uncertainty about appropriateness of data sets and information used to select a dose–response model. It is interesting to observe that although the two approaches (resampling and decision tree) for generating probability distributions for risk estimate seem conceptually quite different, they can be unified under a Bayesian framework. One can consider each of the pathways in a decision-tree approach as a single model, and then apply the Bayesian model averaging concept (e.g. Hoeting et al., 1994; Kang et al., 2000; Bailer et al., 2005; Morales et al., 2006) to construct a Bayesian posterior distribution (we note that our approach in this paper considers only the full multistage model and model averaging approach can also appropriately include different models from the multistage family

of models). Therefore, a Bayesian framework can offer a unified platform not only for deriving probability distributions for a single model, but also an approach to considering several alternative models. Admittedly, however, the challenge of defining a set of models to adequately represent a corresponding sufficient set of plausible biological alternatives still remains, and may prove difficult and controversial.

The methods presented here address the probability distribution of low dose–response for a chosen model. While the methodology presented here can provide much insight into behavior of curve fitting extrapolations to estimate low-dose probabilities, results also serve to emphasize the fundamental limitations of curve fitting approaches. Significant advances in understanding low-dose risks will necessarily come from greater biological understanding of cancer and other toxic events. As this biological understanding increases, modeling approaches such as presented here can play a greater role in quantifying uncertainty in low-dose risk estimation.

For future research, it would be of interest to compare the Bayesian procedure with other likelihood-based resampling approaches such as Bayesian bootstrap (Rubin, 1981) and weighted likelihood bootstrap (Newton and Raftery, 1994). Unlike the original bootstrap, these methods generate likelihood statements about parameters and thus are statistically more comparable to our proposed approach. It is also of interest to provide a more rigorous statistical procedure for analysis of a decision tree generated probability distribution.

We believe that risk assessment community should take full advantages of the fruitful research results in Bayesian analysis and computational power of MCMC, which have become available only recently. These recent advances allow derivation of probability distributions and central estimates of risk and contribute to meaningfully quantifying uncertainties in cancer risk assessments.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yrtph.2007.08.002.

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